Thrombolysis or Heparin Therapy in Massive Pulmonary Embolism With Right Ventricular Dilation*

Results From a 128-Patient Monocenter Registry

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Study objectives: To assess the potential benefit of thrombolysis in patients with massive pulmonary embolism (PE) with stable hemodynamics and right ventricular dysfunction.

Design: Retrospective, cohort study.

Setting: University-based, tertiary referral medical center.

Patients: One hundred fifty-three consecutive patients with massive PE from January 1992 to December 1997 treated with heparin or thrombolysis.

Measurements and results: Massive PE was confirmed by perfusion lung scan or pulmonary angiography. Right ventricular dysfunction was assessed by echocardiography (right ventricular/left ventricular [RV/LV] diastolic diameter ratio > 0.6) in all patients. In order to study a homogeneous population, 64 patients treated with thrombolysis (group 1) were matched on baseline RV/LV diameter ratio to 64 patients treated with heparin (group 2). Perfusion lung scan was repeated at day 7 to day 10. Mean relative improvement in perfusion lung scans was higher in group 1 than group 2 (54% vs 42%, respectively). PE recurrences were the same in both groups (4.7%; n = 3). There were no bleeding complications and no deaths in group 2. Conversely, in group 1, 15.6% (n = 10) of patients suffered from bleeding (4.7%; n = 3 with intracranial bleeding) and 6.25% (n = 4) of them died.

Conclusions: The results of this monocenter registry do not support the indication for thrombolysis in patients suffering from massive PE with stable hemodynamics and right ventricular dysfunction. Appropriate therapy in such patients still remains unknown. Further prospective randomized trials should be performed.

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Key words: heparin; low-molecular-weight heparin; massive pulmonary embolism; right ventricular dysfunction; thrombolysis

Abbreviations: LMWH = low-molecular-weight heparin; PE = pulmonary embolism; RV/LV = right ventricular/left ventricular; UFH = unfractionated heparin

Despite many previous studies1–4 of pulmonary embolism (PE) showing clear improvement of early revascularization with thrombolysis, treatment of massive PE still remains unclear in patients in hemodynamically stable condition. Thrombolysis, if not contraindicated, is the recommended treatment in patients with life-threaten-

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Clinical Investigations
MATERIALS AND METHODS

Patients

From January 1992 to December 1997, 153 consecutive patients with massive PE were admitted to the ICU of the cardiology department and were treated either with thrombolysis (n = 80) or heparin (n = 73).

Inclusion Criteria: Inclusion criteria included (1) PE confirmed by a high-probability perfusion lung scan based on revised Prospective Investigation of Pulmonary Embolism Diagnosis criteria,10 coupled with a positive leg ultrasound test result or by pulmonary angiography in all other cases; (2) Miller index of >40% on perfusion lung scan; and (3) echocardiographic right ventricular dilation, ie, right ventricular/left ventricular diameter (RV/LV) ratio > 0.6 from left parasternal or subcostal view in supine position, and end-diastole, in the absence of left ventricular or mitral valve disease.

Exclusion Criteria: Exclusion criteria included (1) arterial hypotension (defined as systolic BP < 90 mm Hg) with or without peripheral signs of hypoperfusion, (2) syncope prior to hospitalization, (3) usual contraindications to thrombolysis, and (4) necessity of IV inotropic support.

In order to have two comparable groups, patients treated with thrombolytic therapy were matched to those treated with heparin therapy, on baseline echocardiographic RV/LV ratio (according to the chronologic order of hospital admission). Therefore, 64 patients treated with thrombolysis (group 1) were compared to 64 patients treated with heparin (group 2).

Medication

Thrombolysis in group 1 was IV: 100-mg infusion (10 mg of which was injected as a bolus) or 0.6 mg/kg of alteplase over a 2-h period (n = 33), 15,000 IU/kg/20-min of urokinase (n = 20) or 80-mg/1 h infusion of saruplase, 10 mg of which was injected as a bolus (n = 11). IV unfractionated heparin (UFH) was administered at the end of thrombolytic drug perfusion, and was adjusted to keep the activated partial thromboplastin time at two to three times the normal value. In group 2, heparin treatment was as follows: UFH (n = 6), low-molecular-weight-heparin (LMWH, n = 56), and both UFH and LMWH in two cases (n = 2). LMWHs were administered subcutaneously twice daily in the following fixed doses: 100 antifactor Xa/kg units injection of dalteparin (n = 43); 92 antifactor Xa/kg units injection of nadroparin (n = 13); and once-daily 175 antifactor Xa units injection of tinzaparin (n = 2). All patients were treated with oral anticoagulant, warfarin, from day 3 to day 4 on average, adjusted to an international normalized ratio of 2 to 3.

Study Design

For each patient, baseline evaluation included a clinical examination, ECG, transthoracic echocardiography, perfusion lung scan, and conventional pulmonary angiography if needed. Clinical examination and perfusion lung scans were repeated at day 7 to day 10, and earlier in case of clinically suspected recurrence. Efficacy was evaluated on clinical criteria and on perfusion lung scan evolution. Safety was evaluated by bleeding complications. Severe bleedings were defined as intracranial hemorrhage (confirmed by CT), a decrease in hemoglobin level (at least 4 g/100 mL) and bleeding that required surgery or blood transfusion of ≥ 2 U.

Echocardiographic Doppler data were obtained on patients in the supine position by one of three physicians. The diameters of the right and left ventricles were taken in relation to a line perpendicular to left ventricular long axis, at the end of the diastole (beginning of the QRS complex), in parasternal and subcostal views. Right ventricular dysfunction was appreciated with RV/LV ratio; 0.6 was considered as a significant right ventricular overload. Pulmonary artery systolic pressure was calculated as the sum of estimates of the maximum pressure difference between the right ventricle and right atrium (on tricuspid regurgitation Doppler echocardiographic signal) and the estimate of mean right atrial pressure.

Statistical Analysis

The characteristics of the patients in the two groups were compared using the Pearson test for the qualitative variables and Student’s t test for the quantitative variables. Quantitative values are expressed as mean ± SD. The data were analyzed with SPSS software (release 5.0; SPSS; Chicago, IL).11

RESULTS

The baseline characteristics of the two groups of patients were similar, as shown in Table 1. The mean age of the patients was 72 ± 12 years. Approximately 15% of them had a previous PE history. Pulmonary arterial systolic pressure was 56 ± 12 mm Hg, and mean RV/LV ratios were 0.80 and 0.81, respectively. Lung scan defect was higher in group 1 (thrombolysis; 46 ± 10%) than in group 2 (heparin; 43 ± 11%) but without significant difference.

Mean relative improvement in perfusion lung scan defect was significantly higher in group 1 (54%) vs group 2 (42%; p = 0.01). At day 7, perfusion lung scan defect was 21 ± 12% in group 1 vs 23 ± 12% in group 2 (Fig 1). A relative improvement of perfusion lung scan defect > 50% was seen in 57% of patients in group 1 vs 37% in group 2 (Fig 2).

In-hospital results are shown in Table 2. The PE recurrence rate was the same in the two groups (4.7%). All patients survived in group 2, but four

| Table 1—Baseline Characteristics of the 128 Selected Patients* |
|-------------|----------------|----------------|----------------|
| Characteristics | Group 1 (n = 64) | Group 2 (n = 64) | p Value |
| Male/female gender, No. | 25/36 | 25/39 | 0.72 |
| Age, yr | 73 ± 11 | 71 ± 12 | 0.49 |
| Age range, yr | 34–91 | 20–93 | 0.93 |
| Onset of symptoms, d | 13 ± 26 | 11 ± 14 | 0.51 |
| Chronic cardiac disease | 6 (9) | 4 (6) | 0.59 |
| Chronic respiratory disease | 6 (9) | 9 (14) | 0.09 |
| Previous PE | 9 (14) | 11 (17) | 0.01 |
| RV/LV ratio | 0.81 ± 0.12 | 0.80 ± 0.12 | 0.67 |
| PAsP, mm Hg | 56.1 ± 12.4 | 56 ± 12.6 | 0.95 |
| LS defect, % | 46 ± 10 | 43 ± 11 | 0.09 |

*Data are presented as mean ± SD or No. (% unless otherwise indicated. PAsP = pulmonary artery systolic pressure; LS = lung scan.
patients died in group 1 (6.5%): one patient died on day 3 from shock that occurred after thrombolysis, one patient died from PE recurrence with shock on day 3, and two patients died from cerebral bleeding on day 1 and day 5, respectively. Bleedings were significantly lower in group 2 (heparin; no bleeding) vs 15.6% (n = 10) in group 1 (p = 0.001). The bleeding events in group 1 were as follows: three puncture site bleedings, one epistaxis, three intracranial bleedings (two of which were fatal), two GI bleedings, and one occult bleeding leading to RBC transfusion. The difference in severe bleeding rates, as previously defined, was also statistically significant between the two groups: 0% in group 2 and 9.4% in group 1 (p = 0.028). The results of each thrombolytic drug are detailed in Table 3.

The first patient suffering from intracranial bleeding was a 91-year-old woman without any history of hypertension, who was treated with urokinase infusion. Four hours later, she had high systolic BP; intracranial hemorrhage was noticed on CT scan 8 h after the beginning of the infusion, and the patient died 2 h later. The second patient was an 85-year-old woman without any history of hypertension, who was treated with alteplase infusion (0.6 mg/kg/2 h). Systolic hypertension was noticed at day 1, immediately followed by an occipital hemorrhage. She was discharged with visual sequelae. The third patient was a 58-year-old man with prior moderate hypertension, who was treated with alteplase infusion (100 mg/2 h). BP was 160/100 mm Hg on hospital admission. An occipital hemorrhage occurred 13 h after the beginning of infusion, and the patient died on day 5.

The baseline characteristics and hospitalization data of the 25 excluded patients are listed in Table 4. The mean age of the excluded patients was comparable to the mean age of the study group, but the RV/LV ratio was higher, especially in the 15 patients treated with thrombolysis; overall mortality rate was 12% as compared to 3% in the study group.

**Discussion**

Doppler echocardiography is particularly useful for detection of right ventricular dysfunction in severe or massive PE.12,13 RV/LV end-diastolic diameter ratio, though not commonly used in North America, has been validated in various studies as a very sensitive criterion for the diagnosis of PE severity. Comf14 showed a good correlation between the RV/LV end-diastolic diameter ratio measured in parasternal view and the percentage of vascular obstruction. Fournier et al15 showed, in a series of 50

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**Table 2—In-hospital Results**

<table>
<thead>
<tr>
<th>Results</th>
<th>Group 1 (n = 64)</th>
<th>Group 2 (n = 64)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent PE</td>
<td>3 (4.7)</td>
<td>3 (4.7)</td>
<td>1</td>
</tr>
<tr>
<td>Mortality</td>
<td>4 (6.25)</td>
<td>0</td>
<td>0.12</td>
</tr>
<tr>
<td>Bleedings</td>
<td>10 (15.6)</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>Severe</td>
<td>6 (9.4)</td>
<td>0</td>
<td>0.028</td>
</tr>
<tr>
<td>Intracranial</td>
<td>3 (4.7)</td>
<td>0</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).

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**Table 3—Results of Each Thrombolytic Drug Treatment**

<table>
<thead>
<tr>
<th>Results</th>
<th>Alteplase (n = 33)</th>
<th>Urokinase (n = 20)</th>
<th>Saruplase (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>1 (3)</td>
<td>3 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent PE</td>
<td>0</td>
<td>2 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Bleedings</td>
<td>7 (21)</td>
<td>2 (10)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (12)</td>
<td>1 (5)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Intracranial</td>
<td>2 (6)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are presented as No. (%).
patients with a group of massive PE and a group of nonmassive PE (according to pulmonary angiography results), that an RV/LV ratio > 0.6 was observed in 97% of patients with massive PE vs 39% of patients with nonmassive PE. Chapoulot et al showed that the RV/LV diameter ratio was also a good criterion of treatment efficacy in a series of patients with severe massive PE (pulmonary vascular obstruction of 67 ± 10%) treated with thrombolysis, with a decrease from 0.87 ± 0.3 prior to treatment to 0.6 ± 0.3 after treatment (p < 0.001). Patients with right ventricular overload have an increase of relative risk of death from 5 to 7% to about 8 to 10%.

According to some authors, thrombolysis should be used in such patients despite clinical stability and increased bleeding risk. Thus, Konstantinides et al found that overall 30-day mortality was significantly lower in the group of patients treated with thrombolysis than in the group of those treated with IV UFH alone (4.7% vs 11.1%, respectively), but these results were observed in a registry of heterogeneous patients. Many of them had signs of clinical severity: > 40% of patients had arterial hypertension and 25% had syncope. Besides, there were more patients with prior chronic pulmonary disease in the heparin-treated group.

Conversely, in our study, whose clinical efficacy results are not in favor of thrombolysis, the two groups of patients were comparable according to prior history of cardiac or pulmonary disease, right ventricular dysfunction, and perfusion lung scan defect, and all patients were free of clinical signs of severity. Treatment was heterogeneous in group 1, but all thrombolytic regimens were European-approved regimens except for saruplase. Saruplase efficacy and safety have been validated in myocardial infarction, and the same dosage (80 mg over 1 h) has been tested successfully in a series of 20 patients suffering from acute massive PE. Most of the patients of group 2 were treated with LMWHs, the efficacy and safety of which have been validated in the treatment of symptomatic proximal deep venous thrombosis, a situation in which silent PE, sometimes massive, is frequently associated. In two recent trials, LMWHs were compared to IV UFH to treat symptomatic PE: in the study by Simonneau et al, tinzaparin (175 antifactor Xa U/kg subcutaneously qd), and reviparin (twice-daily weight adapted) in the Columbus Investigators study. In the study by Simonneau et al, 28% of patients had severe PE, and 41% of them had lung scan defect > 50%. Efficacy and safety of tinzaparin vs heparin were comparable, with a low severe bleeding rate (0.9% and 1.6%, respectively). In the Columbus Investigators study, about one third of patients (271 patients) had symptomatic PE and there was no difference between the two treatment groups over the 3 months of follow-up with respect to the major clinical outcomes. Also, in opposition to the results of Konstantinides et al, Ribeiro et al, in patients in stable condition suffering from severe PE and treated either with thrombolysis or heparin, found the same in-hospital mortality rate of 8.6% in the two groups.

The only advantage of thrombolysis over heparin found in our study was a higher 1-week perfusion lung scan improvement, as previously observed in the Urokinase Pulmonary Embolism Trial. The in-hospital PE recurrence rate was equivalent in our two treatment groups, as also observed in the Urokinase Pulmonary Embolism Trial.

Severe bleeding rate was higher in the thrombolysis group, and the difference reached statistical significance despite more stringent criteria of definition than in previously published studies. It has to be noted that two deaths out of four in our study resulted from cerebral bleeding in the group of patients treated with thrombolysis. Unfortunately, cerebral bleedings are not exceptional (1.9%) with thrombolysis, as it was reported in a 1997 overview. Our safety data are consistent with the results of this overview. Nevertheless, we have to point out that all cerebral bleedings occurred in high-risk patients (ie, elderly, hypertensive). In 1993, Meneveau et al, following the results of a study comparing thrombolysis between elderly and nonelderly patients suffering from massive PE, concluded that this therapy was as effective and safe in elderly patients as in younger ones. Nevertheless, their population size was probably too limited (36 patients > 70 years old) to assess the bleeding risk with accuracy. Also in 1993, Simonou et al compared the data of 150 patients with documented intracranial hemorrhage following thrombolysis for myocardial infarction to
matched control subjects. They concluded that age > 65 years, systemic hypertension on hospital admission, body weight < 70 kg, and administration of alteplase were independent predictors of cerebral bleeding. A recently published study of thrombolysis in 7,864 patients with myocardial infarction suggests that this therapy is not efficient in patients > 75 years old and may be harmful with a stroke rate of 2.7%, as compared to 1.4% in younger patients. Therefore, thrombolysis should be considered as contraindicated in high-bleeding-risk patients without life-threatening massive PE unless a clear clinical benefit is demonstrated in a prospective randomized trial.

Several limitations have to be considered regarding our study. It is a retrospective study, and the number of included patients is relatively small. But our population is homogeneous with patients matched together on baseline echocardiographic findings. Echocardiography is an obvious and important noninvasive procedure to assess right ventricular dysfunction, but its accurate quantification remains uncertain; it may be that its threshold of severity needs better definition. Finally, to compare the results of these two treatments with hard end points (death, severe bleedings, etc) would require a prospective randomized trial with > 1,000 patients; such a trial would be mandatory to answer the question and would be difficult to perform.

**Conclusion**

Despite several limitations regarding its retrospective design and the small number of included patients, the results of this case-controlled study do not favor thrombolysis in patients suffering from massive PE with stable hemodynamics and right ventricular dysfunction. To demonstrate which treatment, thrombolysis or heparin, has the best efficacy/safety profile will require a large-scale, prospective randomized trial.

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